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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/214,124	LOPEZ LASTRA ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☒ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☒ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 20, 21 and 24 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). For the purpose of compact prosecution, these claims will be treated herein as method claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claim 20 is drawn to a method of preparing a pharmaceutical composition comprising a vector of claim 8, a viral particle generated from a viral vector of claim 8, or a cell comprising a vector or a virus particle generated from a viral vector of claim 8 for the treatment and prevention of a disease which is treatable by gene therapy. Claims 22 and 23 are directed to the same pharmaceutical composition, and in addition an embodiment of claim 22 is drawn to a polypeptide prepared from said vector, said viral particle or said cell with a pharmaceutically acceptable carrier.

The specification discloses the construction of mono- and dicistronic vector plasmids comprising the 5' non-translational leader of avian reticuloendotheliosis virus type A (REV-A) and characterizes the Internal Ribosomal Entry Segment (IRES) within said 5' non-translational leader. It appears that the minimal IRES sequence resides within a fragment (nucleotides 452-578) of the 5' leader. The specification further discloses the construction of series of retroviral vectors comprising the REV-A sequences containing the minimal IRES site. The retroviral vectors possess either Mo-MLV type LTRs (pREV HW vector series) or spleen necrosis virus (SNV) type LTRs (pMC vector series not disclosed). The infectious viral particles generated from these

retroviral vectors were used to determine the viral titer and the expression of reporter genes (placental alkaline phosphatase and neo). The specification teaches that retroviral vectors comprising both a REV-A sequence (nucleotide fragments 265-578 or 452-578) and a conventional encapsidation region (Mo-MLV or VL30) produce viral particles at high titer. Furthermore, it appears that the REV-A sequence ranging from nucleotides 265 to 578 is able to enhance the encapsidation of the viral RNAs and consequently the higher viral titer in comparison with the control vector pEMCV-CBTV comprising the EMCV IRES site. In comparison with the same control vector, the dicistronic retroviral vector pREV HW-3 comprising REV-A IRES sequence 265-578, is significantly more efficient in transducing reporter genes *in vitro* in the human cell line Dev, derived from a human primary tumor of neuroectodermal origin, whose cells behave like pluripotent stem cells. The specification further discloses that the expression of the reporter genes was unaffected by the differentiation state of these Dev cells.

The above evidence is noted and considered. However it can not be extrapolated to the instant claimed invention, which when read in light of the specification is drawn to a pharmaceutical composition and a method of preparing the same to treat and prevent diseases such as, cystic fibrosis, hemophilia A or B, cancer, AIDS, cardiovascular diseases among others (See specification, pages 12-14). The intended use of the claimed invention lies within the realm of gene therapy art.

The specification is not enabled for the intended use of the claimed pharmaceutical composition and method for preparing the same, because at the

effective filing date of the instant application the art of gene therapy is immature and highly unpredictable. In a meeting report on a workshop for gene therapy and translational cancer research (Clin. Cancer Res. 5:471-474, 1999), Dang et al. noted that further advancement in all fields including, gene delivery, gene expression, immune manipulation, and the development of molecular targets is needed to make gene therapy a reality. They further cited the findings of the Orkin-Motulsky Committee (commissioned by the NIH director) which found that human gene therapy is an immature science with limited understanding of gene regulation and disease models for preclinical studies (First paragraph, page 471). Dang et al. pointed out several factors limiting an effective human gene therapy, including, sub-optimal vectors, the lack of long term and stable gene expression, and most importantly the efficient gene delivery to target tissues (last paragraph, page 474).

The breadth of the claims encompasses the use of a vector, a viral particle generated from a viral vector, a cell comprising a vector or a viral particle, or a polypeptide prepared from said vector, viral particle or cell of the instant application to treat various diseases. However, the specification fails to provide sufficient guidance, direction and examples demonstrating the efficacy of the claimed pharmaceutical composition to treat or prevent any disease, and said composition is not even tested in any animal model of any disease for its therapeutic or prophylactic effects. With regard to the composition comprising vector or viral particles, the specification does not teach a skilled artisan the said composition can produce therapeutic or prophylactic proteins/polypeptides in a sufficient amount for a sufficient period of time *in vivo,* to yield

desirable treatment results for a patient. This is a relevant issue since sub-optimal vector continues to be one of several factors limiting the effectiveness of gene therapy as mentioned briefly above. In a review on gene delivery systems (both viral and non-viral vectors), Wivel and Wilson (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501, 1998) stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases.... It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section).

The breadth of the claims also encompasses the expression of any and all genes of interest by the claimed composition in a host for treatment purposes. However, Eck and Wilson (Gene-based therapy, 1996) addressed several specific factors that complicate *in vivo* gene transfer and expression which result in therapeutic effects. These include, the fate of delivering vectors, the fraction of vectors taken up by the target cell population, the rate of vector degradation, the level of mRNA produced, the stability of the protein produced, the protein's compartmentalization within the cell or its secretory fate (Column 1, page 82). Even for localized administration of vectors, the above factors differ dramatically based on the protein being produced, and the desirable therapeutic effect being sought. Therefore, the level of gene expression, its duration,

and its *in vivo* therapeutic effects are not always predictable, and hence without any *in vivo* examples provided by the instant application, it would have required undue experimentation for a skilled artisan to use the claimed invention.

The breadth of the claims also encompasses any and all routes of administering the claimed pharmaceutical composition in a patient for treatment purposes. The specification does not provide sufficient guidance or any example demonstrating that the pharmaceutical composition, in the forms of a vector or viral particles, can be delivered to target cells in an effective amount by any delivery means into a patient to obtain therapeutic or prophylactic effects. Particularly, in the presence of a competent immune response of a patient against most viral vectors. Vector targeting *in vivo* to desired tissues, organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promise, but is currently even less efficient than

viral gene delivery (see page 65, first pargraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239, and second and third columns of page 242). The specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting *in vivo*, such that efficient and effective amount of therapeutic gene transfer is achieved by any mode of delivery. Therefore, it would have required undue experimentation for a skilled artisan to practice the claimed invention.

With regard to the use of a pharmaceutical composition comprising of a cell comprising a vector or viral particles of the instant application for therapeutic purposes, there are similar and additional gene therapy hurdles that one skilled in the art would encounter. These include, the fate of such therapeutic cells once they are delivered into a subject, the duration and expression levels of transgenes of interest in the recombinant cells, and most importantly, the host immune responses against the administered therapeutic cells. It is already well known in the art that a major problem in cell transplantation is rejection of transplanted cells by the host. The instant claims would encompass the use of allogeneic, xenogeneic, as well as autologous genetically modified cells.

At the effective filing date of the instant application, cell transplantation therapies with genetically altered cells to treat diseases and disorders are neither routine nor predictable. As an example, regarding to the utilization of mesenchymal stem cells for human gene therapy, Gerson (Nature Med. 5:262-264, 1999) indicated many questions that need to be addressed, such as, "What is the minimum proportion of donor mesenchymal stem cells required to affect a long-lasting therapeutic response?", "Will. transplantation of mesenchymal stem cells from a marrow harvest or from culture-expansion be sufficient to treat other diseases?", "Can culture-expanded mesenchymal stem cells substitute for fresh marrow allografts in the correction of genetic disorders of the mesenchyme?", "To which host tissues do infused mesenchymal stem cells home, proliferate and differentiate, and using which regulatory signals?", "Can mesenchymal stem cells be used effectively for gene transfer and gene deliver?", "Is systemic infusion optimal or is infusion into a target organ required?" (column 1, second paragraph, page 264). Similar questions and concerns would be raised for the utilization of other genetically modified cells encompassed by the breadth of the claimed pharmaceutical composition in the instant application for therapeutic or prophylactic purposes.

Accordingly, due to the lack of direction, guidance presented in the specification regarding to the use of the claimed pharmaceutical composition, process of preparing the same in treating or preventing diseases in a patient, the absence of working examples, the breadth of the claims, and the state and the unpredictability of the gene therapy art, it would have required undue experimentation for one skilled in the art to use the claimed invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mono- or dicistronic vector for the expression of one or more genes of interest comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, wherein said nucleotide sequence acts as an entry site in a vector and for encapsidation of a retroviral vector, a viral particle generated from the same vector and a method of incorporating said nucleotide sequence into the mono- or dicistronic vector, does not reasonably provide enablement for any and all polycistronic vector for the expression of one or more genes of interest comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of any and all type C retrovirus, wherein said nucleotide sequence acts as an internal ribosomal entry site and for encapsidation of a retroviral vector, a viral particle generated from said polycistronic vector and a method for incorporating said nucleotide sequence into the polycistronic vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a vector for the expression of one or more genes of interest comprising a nucleotide sequence derived from all or part of the 5' end of the gnomic RNA of a type C retrovirus with the exception of the Friend (FMLV) and Moloney (MoLV) murine leukemia viruses, as internal ribosome entry site in a vector and for the

encapsidation of a retroviral vector, a viral particle generated from said vector and a method of incorporating said nucleotide sequence into said vector.

The specification is not enabled for such a broadly claimed invention. This is because the specification fails to provide sufficient guidance or direction and examples of vectors comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of any and all type C retrovirus other than those derived from REV, MSV, FMLV or MoLV, in which said nucleotide sequence acts as an IRES site and for encapsidation of a retroviral vector. At the effective filing date of the instant application, nucleotide sequences acting as IRES sites and for encapsidation of a retroviral vector for type C retrovirus such as MEV, FMOV, AMLV, MEELV, GALV, BAEV and others (encompassed by the breadth of the claims) have not been identified. In addition, the specification fails to teach the construction of any polycistronic vector (other than a bicistronic vector) comprising the 5' end of a type C retrovirus genome, nor set forth all the elements (encapsidation region, internal promoter region, genes of interest) and their orientation in such a vector. Without such guidance and direction, it would have required a skilled artisan undue experimentation to attain a polycistronic vector efficient for its expression of genes of interest and high viral titer in the case of a viral vector. As an example, Lopez-Lastra et al. (Hum. gene ther. 8:1855-1865, 1997) noted that even for bicistronic retroviral vectors pREV-HW3 and pREV-HW2, their recombinant retroviral titers are variable because of the selective interaction between the REL-A E sequence and the VL30 sequence located in the same transcriptional unit. Furthermore, Lopez-Lastra et al. also stated that "Possible interactions taking place between REV-A E and

MLV E+ both in MLV- and SNV- based retroviral vectors are currently under study." (Column 2, first paragraph, page 1863).

Accordingly, due to the lack of direction, guidance and examples presented in the specification regarding to polycistronic vectors comprising 5' end of a type C retrovirus genome, the unpredictability of the interactions among various components within a polycistronic vector, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to use the broadly claimed invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing one or more polypeptides of interest *in vitro* using a mono- or dicistronic vector comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, a viral particle generated from a viral vector comprising the same features or a cell comprising said vector or said viral vector, does not reasonably provide enablement for a method of preparing one or more polypeptides of interest by any and all recombinant routes, or a method for the production of a transgenic animal using vector of claim 8, a viral particle generated from a viral vector of claim 8 or cell comprising the same vector or viral particle. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claim is directed to a method for preparing one or more polypeptides of interest by the recombinant route or for the protection (This is probably an inadvertent error, applicants probably mean production) of a transgenic animal using a vector of claim 8, a viral particle generated from a viral vector of claim 8 or a cell comprising a vector or a viral vector of claim 8.

When read in light of the specification (Page 18, lines 13-24), the claimed method for preparing one or more polypeptides of interest encompasses the production of a transgenic animal whose genome comprises a cassette for the expression of one or more genes of interest, and the harvest of the polypeptides of interest from the biological fluids of said transgenic animal, using the vector, viral particle or cell of the instant claimed invention. The specification is not enabled for such broadly claimed invention, because at the effective filing date of the instant application, the art of transgenesis is highly unpredictable. The specification fails to provide any guidance or direction or examples regarding to the production of any type of transgenic animal, let alone, the harvest of polypeptides of interest from the biological fluids of said transgenic animal. The specification merely recites that "The techniques for generating these transgenic animals are known. The polypeptide of interest may be recovered in a conventional manner, for example, from the biological fluids (blood, milk and the like) of the animal (page 18, lines 20-24). The specification fails to set forth any parameters or conditions for the generation of any kind of transgenic animal, for examples, therapeutic gene constructs available for use, promoters used for the expression of therapeutic gene products into the biological fluids of a transgenic animal, among others. Mullins et

al. (J. Clin. Invest. 98:S37-S40, 1996) have noted the positional effects due to the random integration of exogenous DNA into chromosomal DNA have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene (column 2, first paragraph, page S37). Because of the unpredictable nature of random transgene integration and positional effects, it would be extremely difficult to predict successful transgene transfer and its expression in any transgenic animal. The breadth of the instant claim encompasses any and all transgenic animals. However, it is well known in the art, that the production of transgenic animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. This observation is supported by Seamark (Reprod. Fert. Dev. 6:653-657, 1994) by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (Page 6, Abstract). Likewise, Mullins et al. stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (Page S38, column 1, first paragraph). Mullins et al. further stated that "a given construct may react very differently from one species to another." (Page S39, summary). Wall (Theriogenology 45:57-68, 1996) supported this observation by stating that "Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." (Page 61, last paragraph) and "transgene expression and the physiological consequenes of

transgene products in livestock are not always predicted in transgenic mouse studies." (Page 62, first paragraph).

Accordingly, due to the lack of direction, guidance and examples presented in the specification regarding to the use of a composition comprising a vector, viral particle or transfected cell of the instant claimed invention for the generation of transgenic animal for preparation of one or more polypeptides of interest, the breadth of the claims, the state and the unpredictability of the transgenic art, it would have required undue experimentation for one skilled in the art to make and use the broadly claimed invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transfection or infection of pluripotent cells *in vitro* using a mono- or dicistronic vector comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, a viral particle generated from a viral vector comprising the same features, does not reasonably provide enablement for the same method *in vivo* or the use of a pharmaceutical composition comprising a vector of claim 8 or a viral particle generated from a viral vector of claim 8 in the same method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claim is drawn to a method of transfection or infection of pluripotent cells, preferably pluripotent cells of the central nervous system, using a vector or a viral

particle generated from a viral vector of claim 8, or a pharmaceutical composition comprising said vector or said viral particle.

The specification is not enabled for such a broadly claimed invention. The breadth of the claim encompasses both *in vitro* and *in vivo* transfection or infection of pluripotent cells. When read in light of the specification, the intended use for the *in vivo* transfection or infection of pluripotent cells using a vector or a viral particle of the instantly claimed invention is solely for treatment purposes. The specification fails to provide guidance or direction and examples demonstrating the infection of any pluripotent cells *in vivo* using a vector or viral particle of the instantly claimed invention. The specification has not set forth conditions, parameters for one skilled in the art to overcome all the hurdles outlined in the rejection of claims 20, 22 and 23 above to practice this claimed invention, particularly with respect to the pharmaceutical embodiment of the claim.

Accordingly, due to the lack of direction, guidance and examples presented in the specification regarding to the *in vivo* use of a claimed composition comprising a vector or viral particle of the instant claimed invention, the breadth of the claim, the state and the unpredictability of the gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the broadly claimed invention.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 8-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of using a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus with the exception of FMLV and MoLV, as internal ribosome entry site (IRES) in a vector and for the encapsidation of a retroviral vector, a vector for the expression of one or more genes of interest comprising said nucleotide sequence and methods of using the same vector. The broadest claims read on a method of using a nucleotide sequence derived from the 5' end of the genomic RNA of type C retroviruses such as, MHV, MEV, FMOV, AMLV, MEELV, SFFV, RASV, FLV, FSV, EFLV, SSV, GALV, BAEV and others, and a polycistronic retroviral vector comprising at least three genes of interest and at least one of the encapsidation and the IRES site consist of a nucleotide sequence derived from all

or part of the 5' end of the genomic RNA of a type C retrovirus with the exception of the FMLV and MoMLV. The specification fails to describe and demonstrate the exact nucleotide sequences derived from type C retroviruses such as MEV, FMOV, AMLV, MEELV, GALV, BEAV and others, with the exception of FMLV, MoMLV, MSV and REV (demonstrated by the instantly claimed invention), to act as IRES sites and for encapsidation of a retroviral vector. Additionally, the state of the art was that such functional information was not available. Furthermore, the specification fails to provide sufficient information regarding the construction of any polycistronic vector comprising at least three genes of interest and a 5' end of a type C retrovirus. Teachings on the nucleotide sequences of genes of interest, internal promoters to be utilized and the orientation of various structural components in said polycistronic vector are not adequately provided. Therefore, it would have required a skilled artisan undue experimentation to attain a polycistronic vector efficient for its expression of the genes of interest and high viral titer. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the claimed polycistronic vector comprising at least three genes of interest and a 5'

end of a type C retrovirus, or the precise nucleotide sequences derived from the genomic RNA of a type C retrovirus with the exception of FMLV, MSV, MoMLV and REV necessary to carry out the claimed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the term "and/or" is unclear and renders the claim indefinite. Is the isolated nucleotide sequence of the instant claimed invention used as internal ribosome entry site (IRES) in a vector or for encapsidation of a retroviral vector or both? Clarification is requested.

The term "improving" in claim 1 is a relative term which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. To which retroviral vectors that the encapsidation of a retroviral vector in the instant application is improved in comparison with?

Also in claims 1 and 4, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1 and 4 recite the broad recitation vector and genomic RNA of an avian reticuloendotheliosis virus, respectively, and the claims also recite retroviral vector and particularly type A, respectively, which is the narrower statement of the range/limitation.

In claims 1, and 3-5, the phrase "part of" is unclear and indefinite. The metes and bound of the claims can not be determined because of the ambiguity of such a phrase. Clarification is needed.

In claim 9, it is unclear what is encompassed by the phrase "characterized in". Which other characteristics does the claimed vector comprise or not comprise? It is suggested that the phrase - - wherein - - is used instead. Also in claim 9, the Markush language is improper. It should be - - selected from a group consisting of ... - -.

In claim 10, the term "and/or" is unclear. Is the nucleotide sequence used to improve the encapsidation of the vector? Or is it used as an IRES site? Or is it used for both purposes? Clarification is required. Also in claim 10, The term "improving" is a relative term which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claim 12, the term "optionally" renders the claim indefinite. Does the claimed retroviral vector contain elements stated in (c) or not? Otherwise, the metes and bound of the claim can not be determined.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as

to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation a murine retrovirus, and the claim also recites MoMLV, which is the narrower statement of the range/limitation. Claims 15-18 also recite the broad recitation starting at nucleotide 265 and ending at nucleotide 578, or at nucleotide 1 and ending at nucleotide 578, or an REV virus or an interleukin, and the claims also recite starting at nucleotide 452 and ending at nucleotide 578, starting at nucleotide 265 and ending at nucleotide 578 and especially SNV and IL-2, which are the narrower statements of the range/limitation. Similarly, claims 23 and 24 recite the broad recitation, between 10^4 and 10^{14} pfu and pluriotent cells, and the claims also recite preferably 10^6 and 10^{11} pfu and especially pluripotent cells of the central nervous system, which are the narrower statements of the range/limitation.

In claim 20, the term "and/or" is unclear and indefinite. Is the preparation used for the treatment or the prevention or both? Which one? Clarification is required.

In claim 21, the phrase "for the protection of a transgenic animal" is unclear. It appears that the Applicants probably mean - - for the production of a transgenic animal

- -. For the purpose of compact prosecution of this claim, the latter meaning is taken into consideration.

Claims 1-7, 20, 21 and 24 provide for the use of a nucleotide sequence, a vector or a cell comprising a vector but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 8-10, 12, 18, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Berlioz et al. (J. Virol. 69:6400-6407, 1995).

The claims are drawn to a method of preparing a vector using a nucleotide sequence derived from all or part of the 5'end of the genomic RNA of a type C retrovirus with the exception of the Friend and Moloney murine leukemia virus as internal ribosome entry site (IRES) and for encapsidation of a retroviral vector. The claims are also directed to a vector comprising said nucleotide sequence to be used for

encapsidation of the vector into a viral particle and as an IRES site, and one or more genes of interest. Claim 18 is specifically directed to said viral particle, whereas claim 19 is drawn to a cell comprising the same vector or viral particle. An embodiment of claim 22 is drawn to a pharmaceutical composition comprising the same vector, viral particle or a cell in combination with a pharmaceutically acceptable vehicle. With regard to claim 22, the intended use of a pharmaceutical composition is not given any patentable weight in view of prior art.

Berlioz et al. disclosed the preparation of monocistronic and dicistronic plasmid DNA constructs comprising the rat VL30 region of the Harvey murine sarcoma virus (a member of the type C retrovirus family) leader, and demonstrated that the rat VL30 region serves as an IRES site and efficiently directs the expression of a 3'cistron *in vitro* and *in vivo* (See Figs. 1, 3, 5 and 7). Berlioz et al. also disclosed the construction of a dicistronic MLV-derived retroviral vector, pVL-CBT2, comprising the VL30 sequence (nucleotides 205 to 794) inserted between phosphatase and neomycin genes. Recombinant viral particles that were generated from the transient transfection of pVL-CBT2 viral vector into ecotropic GP-E+86 helper cells were used to infect NIH-3T3 cells to demonstrate that the 5' VL30 sequence provides an IRES for efficient translation of the neomycin gene positioned downstream of said sequence, and for packaging of RNA into MLV virions (See Fig. 8 and column 2, page 6405). Since sterile water and culture media, in which vectors and transfected cells are normally dispersed in respectively, are considered to be pharmaceutically acceptable carrier, the teachings of Berlioz et al. met

all the criteria in the claims. Therefore, the reference clearly anticipates the claimed invention.

Claim 22 is rejected under 35 U.S.C. 102(e) as being anticipated by Hora et al. (U.S. Patent No. 5,997,856).

Claim 22 contains an embodiment drawn to a polypeptide prepared from the vector, viral particle or cell of the instantly claimed invention, in combination with a pharmaceutically acceptable vehicle. The means to produce the claimed polypeptide is not given any patentable weight, because regardless how it is produced, it is still the same polypeptide.

Hora et al. dislosed an aqueous composition comprising an IL-2 polypeptide (See column 12, first paragraph and claims 10-24). The IL-2 polypeptide is in an aqueous composition that is suitable as a pharmaceutical vehicle. Thus, the reference clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8-12, 17-19, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berlioz et al. (U.S. Patent No. 5,925,565) in view of Berlioz et al. (J. Virol. 69:6400-6407, 1995).

The claims are drawn to a method of preparing a vector using a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus with the exception of the Friend and Moloney murine leukemia virus as internal ribosome entry site (IRES) and for encapsidation of a retroviral vector. The claims are also directed to a vector comprising said nucleotide sequence to be used for encapsidation of the vector into a viral particle and as an IRES site, and one or more genes of interest. Claim 18 is specifically directed to said viral particle, whereas claim 19 is drawn to a cell comprising the same vector or viral particle. An embodiment of claim 21 is drawn to a method for preparation of one or more polypeptides of interest by the recombinant route using a vector, viral particle or cell of the instant claimed invention. An embodiment of claim 22 and claim 23 are drawn to a pharmaceutical composition comprising the same vector, viral particle or a cell in combination with a pharmaceutically acceptable vehicle, and wherein it comprises between 10^4 and 10^{14}

pfu. With regard to claims 22 and 23, the intended use of a pharmaceutical composition is not given any patentable weight in view of prior art.

Berlioz et al. disclosed a polycistronic vector (including retroviral vector), a viral particle, an isolated cell comprising the recombinant vector or viral particle, and a method for incorporating a DNA encoding a protein of interest into a cell *in vitro*, that have all the limitations of the claims, except that the IRES site and the encapsidation region of the VL30 murine retrotransposon is not explicitly stated to be derived from the 5' end of the genomic RNA of a type C retrovirus (See claims and Figs. 2 and 3). However, in an earlier reference (J. Virol. 69:6400-6407, 1995), Berlioz et al. disclosed the identical VL30 region can be obtained from the Harvey murine sarcoma virus (HaMSV) leader, and HaMSV is a member of the type C retrovirus family (See page 640). Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berlioz et al. (J. Virol. 69:6400-6407, 1995) in view of Dirks et al. (U.S. Patent No. 6,060,273).

The claim is drawn to a vector of claim 8 comprising a gene of interest encoding a product selected from factor VIII, factor IX, the CFTR protein, dystrophin, insulin, alpha-, beta-, gamma interferon or an interleukin, and a selectable marker.

Berlioz et al. disclosed the construction of a dicistronic MLV-derived retroviral vector, pVL-CBT2, comprising the VL30 sequence (nucleotides 205 to 794) of the Harvey murine sarcoma virus (a member of the type C retrovirus family) leader inserted

between phosphatase and neomycin genes. Berlioz et al. further taught that the 5' VL30 sequence functions as an IRES for efficient translation of the neomycin gene positioned downstream of said sequence, and for packaging of RNA into MLV virions (See Fig. 8 and column 2, page 6405). The disclosed vector of Berlioz et al., however, does not comprise a gene encoding for a product selected from factor VIII, factor IX, the CFTR protein, dystrophin, insulin, alpha-, beta-, gamma interferon or an interleukin. However, Dirks et al. disclosed multicistronic expression units in which the cistrons comprise genes encoding factor VIII, creatine kinase, haemoglobin, scatter factor among others (See claim 9).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a dicistronic MLV-derived retroviral vector of Berlioz et al. with the teachings of Dirk et al. by substituting a gene encoding phosphatase with one encoding factor VIII. The motivation for one of skill in the art to carry out such modification is to produce recombinant factor VIII subunits for preparation of pharmaceutical composition to treat blood disorders. Thus, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, J.D., may be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

QN

Quang Nguyen, Ph.D.

Examiner, AU 1632

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER